UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,726	04/08/2004	Michael Wayne Graham	023004.0104N4US	1523

32042 7590 11/06/2007

PATTON BOGGS LLP
8484 WESTPARK DRIVE
SUITE 900
MCLEAN, VA 22102

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
11/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,726	GRAHAM ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007 and 06 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34 and 88-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34 and 88-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Third-party submission filed under 37 CFR 1.99

A third-party submission has been filed under 37 CFR 1.99 on February 27, 2007 in the published application.

To ensure that a third-party submission does not amount to a protest or pre-grant opposition, 37 CFR 1.99 does not permit the third party to have the right to insist that the examiner consider any of the patents or publications submitted. Furthermore, if the submission or part of the submission is not in compliance with 37 CFR 1.99, that noncompliant submission or part thereof will not be entered in the application file. Therefore, unless the examiner clearly cites a patent or publication on form PTO-892, Notice of References Cited and such reference is used in a rejection or its relevance is actually discussed during prosecution, consideration by the examiner of any patent or publication submitted in a third-party submission cannot be presumed.

If the applicant wants to ensure that the information in a third-party submission is considered by the examiner, the applicant should submit the information in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98. An individual who has a duty to disclose under 37 CFR 1.56 should also submit any material information contained in a third-party submission to the Office in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98 to ensure such material information is properly disclosed to the examiner.

Claim Objections

Claims 94, 100, 101, 112 and 117 are objected to because of the following informalities: in claim 94 the word "single-stranded" is misspelled in line 2, in claim 100 the word "nucleotides" is misspelled in line 2, in claim 112 the word "genome" is misspelled in line 2. Claim 101 contains the phrase "the target gene correspondence to", it appears the word "correspondence" is supposed to be "corresponds" and claim 117 contains the word "single+stranded", it appears that this is supposed to be "single-stranded". Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34 and 88-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US 5,605,559, of record) in view of Agrawal et al. (WO 94/01550, of record) and Chatterjee et al. (US 5,474,935).

The claimed invention is directed to methods of producing RNA in an isolated cell by introducing a genetic construct having two copies of a structural gene wherein one copy is in the sense orientation and the second copy is in the antisense orientation and the construct comprises a promoter and terminator including a polyadenylation signal

and the two copies of the structural gene are separated by a stuffer sequence. Specific embodiments define the target gene, the portion of the gene being targeted, the cell, the length of the stuffer fragment, the size and orientation of the gene copies and the route of delivering the construct to the cell. Claims 104 and 125 contain the limitation that the stuffer fragment comprises an intron. Applicants point to page 19, lines 25-29 as providing support for this limitation. This portion of the specification states that when the multiple structural gene units comprise intron/exon splice junction sequences, the stuffer fragment may serve as an intron sequence. Therefore, the stuffer fragment of claims 104 and 125 is not defined as a particular sequence within the stuffer fragment, but is defined in terms of sequences within the structural gene units. For the purposes of examination, these claims are interpreted as limited to those embodiments wherein one of the known intron/exon splice junction sequences is present in the copies of the structural gene.

Fire et al. teach a method of inhibiting gene expression in cells, including animal cells and plant cells, using double stranded RNAs. The double stranded RNA comprises a sequence complementary to a portion of the target gene and a sequence identical to a portion of the target gene. At column 4, lines 41-46 Fire et al. teach that dsRNAs used in the invention can be formed from a single self-complementary RNA and can include modified nucleotides. At columns 8-9, Fire et al. teach that RNA synthesis can be initiated *in vivo* or *in vitro*, can be expressed from a vector and the expression vectors can comprise regulatory regions including promoters, terminators and polyadenylation signals. Fire et al. additionally teach at column 9 that the dsRNA can be introduced to a cell in a variety of ways, including by lipid-mediated transport

(i.e., a liposome) or within a viral particle. At column 10 Fire et al. teach that viruses can be targeted, including HIV. Fire et al. teach that the dsRNAs can have a length of 25-400 nucleotides. While Fire et al. teach at columns 21-22 that a single promoter can be used to express an inverted duplication of a self-complementary dsRNA, they do not explicitly teach that this RNA comprises a stuffer fragment nor do they teach the inclusion of an intron sequence. At column 5 Fire et al. teach that the dsRNA can target any gene and is not limited to any particular portion of the gene but do not explicitly teach targeting of the untranslated regions of a gene.

It was well known in the art at the time the invention was made that self-complementary nucleic acids form hairpin structures that routinely contain unpaired loop regions. For example, Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On page 15 Agrawal et al. teach that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region and may comprise an unpaired loop region.

At the time the invention was made the person of ordinary skill in the art recognized that untranslated regions of genes are suitable targets for nucleic acid therapeutics. Chatterjee et al. teach constructs targeted to viral genes, explicitly teaching that lentiviruses such as HIV and DNA viruses such as HSV are suitable targets, teaching at column 4 that any viral gene whose sequence is known can be targeted. One of ordinary skill in the art would recognize that this includes the genes for coat proteins and polymerases. At column 3 Chatterjee et al. teach that antisense oligonucleotides targeted against areas of critical viral RNA transcripts including the 5'-

untranslated region, splice sites, and the polyadenylation signal have demonstrated significant antiviral activities.

It would have been obvious to one of ordinary skill in the art at the time of invention to use the method taught by Fire et al. of inhibiting gene expression using self-complementary double stranded RNA expressed from a vector under control of a single promoter to produce RNA 30 nucleotides in length and to include a hairpin loop within the RNA. One of ordinary skill in the art would recognize based on Fire et al.'s teaching of double stranded RNA of 25-400 nucleotides that production of RNA with 30 complementary nucleotides is mere design choice that would be performed in the course of routine optimization and would further recognize that any 30 nucleotide sequence, including one containing intron/exon splice sites, is also a matter of design choice. Based on the teachings of Agrawal of hairpin RNA structures that comprise unpaired loops, one of ordinary skill would recognize that inclusion of a loop region and the number of nucleotides within the loop is a matter of design choice. It would have been further obvious to produce RNA targeted to a viral gene and to target the untranslated regions of the gene. Chatterjee et al. provide a motivation to target an untranslated region of a gene by teaching that targeting of such regions is proven to provide significant antiviral activity.

Because the combination of the cited references provides a vector having the structural limitations of the claims and because administering this vector to a cell as taught by Fire et al. for the purpose of inhibiting gene expression would necessarily result in the production of a RNA capable of delaying, repressing or reducing expression

of a target gene the invention of claims 34 and 88-133 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

The previously applied 103 rejection is withdrawn in view of the newly submitted claims; therefore the arguments presented in the response of November 30, 2006 are moot and only those that might apply to the newly applied rejection have been addressed.

In arguments presented regarding use of the Zhang et al. reference in the previously applied 103 applicants note they are not aware of any case from the courts that adopted the concept of "inherent obviousness". While the reference of Zhang et al. is no longer part of the rejection of record, applicants are referred to MPEP 2112, which states that "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." quoting *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995).

Applicants note that claim 34 has been amended and new claim 114 added to recite a method for producing an RNA molecule cell as a synthetic genetic construct having a particular configuration of elements and assert that Fire et al. neither teach nor contemplate the use of a stuffer fragment to spatially separate two copies of the structural gene and do not disclose the length limitation of 30 nucleotides, the combination of the two copies each having 30 nucleotides, or the combination of all the elements in the order claimed. This argument is not persuasive because while it is correct that Fire et al. do not explicitly teach the presence of a loop region within a self-

complementary RNA, the routine inclusion of loops within a hairpin is routinely used as evidenced by Agrawal et al. and well within the skill of those in the art. The production of RNA of any particular length is also well within the skill of those in the art and use of a particular length is a matter of routine design choice.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

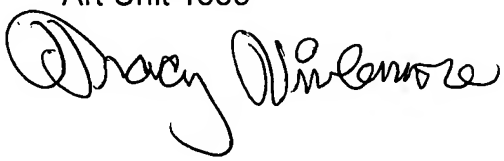
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635



TV
November 1, 2007